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STUDY DESIGN

Telemedical Interventional Management in Heart Failure II (TIM-HF2), a randomised, controlled trial investigating the impact of telemedicine on unplanned cardiovascular hospitalisations and mortality in heart failure patients: study design and description of the intervention

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Background Heart failure (HF) is a complex, chronic condition that is associated with debilitating symptoms, all of which necessitate close follow-up by health care providers. Lack of disease monitoring may result in increased mortality and more frequent hospital readmissions for decompensated HF. Remote patient management (RPM) in this patient population may help to detect early signs and symptoms of cardiac decompensation, thus enabling a prompt initiation of the appropriate treatment and care before a manifestation of HF decompensation.

Objective The objective of the present article is to describe the design of a new trial investigating the impact of RPM on unplanned cardiovascular hospitalisations and mortality in HF patients.

Methods The TIM-HF2 trial is designed as a prospective, randomised, controlled, parallel group, open (with randomisation concealment), multicentre trial with pragmatic elements introduced for data collection. Eligible patients with HF are randomised (1:1) to either RPM + usual care or to usual care only and are followed for 12 months. The primary outcome is the percentage of days lost due to unplanned cardiovascular hospitalisations or all-cause death. The main secondary outcomes are all-cause and cardiovascular mortality.

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Conclusion The TIM-HF2 trial will provide important prospective data on the potential beneficial effect of telemedical monitoring and RPM on unplanned cardiovascular hospitalisations and mortality in HF patients.
Trial registration: ClinicalTrials.gov Identifier NCT01878630.

Keywords Chronic heart failure • Telemonitoring • Remote patient management • Hospitalisation

Introduction

Modern heart failure (HF) care programmes focus on the improvement of ambulatory HF care to reduce the risk of recurrent HF hospitalisations.[1] In the year following a HF hospitalisation, the rate of hospital readmission is approximately 50% and the 1-year mortality rate is 15–20%.[1,2] Current telemedicine HF concepts are holistic programmes which include telemonitoring and telemedical interventions, guideline-based ambulatory care and structured patient education grouped together and known as remote patient management (RPM).[3]

Many randomised controlled trials have investigated the impact of RPM in HF patients on different clinical outcomes — including BEAT-HF,[4] CardioBBEAT,[5] TIM-HF,[6,7] REM-HF,[8] OptiLink HF,[9] IN-TIME,[10] and CHAMPION.[11] The results from these studies are not consistent between each other with respect to morbidity and mortality. This may be explained by the differences in RPM interventions used and the nature of the heterogeneous patient populations included in the studies. Despite the differences in the study designs and the RPM interventions used (including invasive or non-invasive telemonitoring), one suggestion is that unstable HF patients with a recent (i.e. $\leq$ 12 months) hospitalisation for HF before starting RPM appear to have a subsequent lower HF readmission rate, have reduced mortality and an improvement in quality of life. A recent meta-analysis suggests that nurse home visits and disease management clinics can decrease all-cause mortality and readmissions after a recent hospitalisation for HF.[12]

In 2016, the European Society of Cardiology (ESC) recommended class IIb for telemonitoring with invasive telemedical devices in the actual guidelines for the treatment of acute and chronic HF.[13] A meta-analysis of data from completed clinical trials evaluating haemodynamic-guided care for HF patients concluded that haemodynamic-guided HF management using permanently implanted sensors and frequent evaluation of filling pressures was superior to traditional clinical management strategies in reducing the risk of hospitalisations in patients who remain symptomatic.[14]

The TIM-HF trial[6,7] enabled us to critically appraise the procedures and processes which were implemented for this trial, and based on the lessons learnt, we proceeded to design the Telemedical Interventional Management in Heart Failure II (TIM-HF2) trial. The TIM-HF2 trial is designed to assess the impact of RPM on mortality and morbidity in a HF population, also taking into consideration regional settings (i.e. rural vs. metropolitan). We present the design of the TIM-HF2 trial in addition to providing a description of the RPM system and approach which we plan to use in this study.

Study design

The TIM-HF2 trial is a prospective, randomised, controlled, parallel group, open (with randomisation concealment), multicentre trial with pragmatic elements introduced for data collection (ClinicalTrials.gov Identifier: NCT01878630). The study conduct is guided by good clinical practice (GCP), in accordance with the Declaration of Helsinki and the laws and regulations applicable in Germany. Written approval from the appropriate Ethics Committees is required and each patient must provide written informed consent. The TIM-HF2 Steering Committee (see online supplementary *Appendix S1*) and TMC staff members designed the trial and wrote the study protocol. An independent Data Safety Monitoring Board (DSMB) reviewed patient data periodically, as defined in the DSMB charter. A Clinical Endpoint Committee (CEC), blinded to treatment allocation, is appointed to adjudicate all deaths and hospitalisations using pre-defined criteria as detailed in the CEC charter (see online supplementary *Appendix S2*).

Study population, recruitment and randomisation

Eligible patients are patients with HF, with a history of a HF hospitalisation within 12 months prior to randomisation. At the time of randomisation, patients must be in New York Heart Association (NYHA) class II or III with either left ventricular ejection fraction (LVEF) $\leq$ 45% or, if LVEF > 45%, patients must be treated with oral diuretics. The inclusion and exclusion criteria are shown in *Table 1*.

In total, 113 sites located in 14 metropolitan areas with more than 200 000 inhabitants and/or with a medical university (i.e. Berlin, Dresden, Hamburg, Stuttgart, Frankfurt am Main, Leipzig, Hannover), and in 11 rural areas in Germany (namely: Brandenburg, Bavaria, Thuringia, Saxony, Saxony-Anhalt, Hesse, Baden-Württemberg, Lower Saxony, Mecklenburg-Western Pomerania, North Rhine-Westphalia, Saarland) are included. Forty-three sites are hospitals, 10 sites are university hospitals, and 60 sites are local cardiologist practices. In addition, 87 general practitioners (GPs) collaborate in the study by screening and following up their patients (for the list of all involved primary site investigators, see online supplementary *Appendix S3*).

Patients are randomised to either RPM + usual care (RPM group) or to usual care only (UC group) via a secure web-based randomisation system located at the Clinical Trial Centre Leipzig (CTC). To achieve a balance of potential risk factors in the treatment arms, Pocock's minimisation algorithm was used,[15] utilizing 12 baseline variables with 10% residual randomness (see online supplementary *Table S1*).

Table 1 Main inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Diagnosed with HF – NYHA class II or III • Echocardiographically determined left ventricular ejection fraction ≤ 45% or > 45% + oral diuretic prescribed • Hospitalisation due to decompensated HF within the last 12 months before randomisation • Depression score PHQ-9 < 10 • Written informed consent obtained	• Hospitalisation within the last 7 days before randomisation • Implanted cardiac assist system • Acute coronary syndrome within the last 7 days before randomisation • High urgent listed for heart transplantation • Planned revascularisation, transcatheter aortic valve implantation, MitraClip and/or CRT implantation within 3 months after randomisation • Revascularisation and/or CRT implantation within 28 days before randomisation • Known alcohol or drug abuse • Terminal renal insufficiency with haemodialysis • Impairment or unwillingness to use the telemonitoring equipment (e.g. dementia, impaired self-determination, lacking ability to communicate) • Existence of any disease reducing life expectancy to less than 1 year • Age < 18 years • Pregnancy • Participation in other treatment studies or remote patient management programmes (register studies possible)

CRT, cardiac resynchronisation therapy; HF, heart failure; NYHA, New York Heart Association; PHQ, Patient Health Questionnaire.

The RPM intervention consists of the following elements:

- A daily transfer of body weight, blood pressure (systolic/diastolic), heart rate, analysis of the heart rhythm as derived from a 2 min 3-channel electrocardiogram (ECG), peripheral capillary oxygen saturation (SpO_2) and a self-rated health status (scale range 1–5)
- Identification of a patient risk category using the baseline and follow-up visit biomarker values
- Patient education, and
- Cooperation between the telemedical centre (TMC), the patient's GP and cardiologist ('doc-to-doc telemedical scenario') with respect to patient management.

Patients randomised to the UC group are followed in accordance with the current standards (i.e. ESC guidelines for HF management) at the discretion of their treating physicians.[13]

Study assessments and follow-up

The planned follow-up per patient is 365 days and five outpatient visits are scheduled over this time period. After randomisation, outpatient visits are planned at 3, 6, and 9 months and the final study visit should be performed at 365 + 28 days — i.e. up to maximally 393 days post-randomisation (*Figure 1*). The assessments performed at each visit are displayed in *Table 2*.

Home telemonitoring system

In accordance with the study protocol, the home telemonitoring system should be installed in the patient's home within 7 days of randomisation. The RPM system used is based on a Bluetooth system with a digital tablet (Physio-Gate® PG 1000, GETEMED Medizin- und Informationstechnik AG) as the central structural element to transmit vital measurements from the home of the patient to the TMC at the Charité - Universitätsmedizin Berlin. Four measuring devices are part of the system: a 3-channel ECG device to collect a 2 min or streaming ECG measurement (PhysioMem® PM 1000 GETEMED Medizin- und Informationstechnik AG), a device to collect peripheral capillary oxygen saturation (SpO_2; Masimo Signal Extraction Technology (SET®), a system to collect blood pressure (UA767PBT, A&D Ltd.) and a body weighing scales (Seca 861, seca GmbH & Co KG). Each device is equipped with a Bluetooth chip and connected to the digital tablet.

The TMC software used is 'Fontane' (eHealth Connect 2.0, T-Systems International GmbH), which was specifically developed for use in the TIM-HF2 study. The key innovation of Fontane is a novel self-adapting TMC middleware, which consists of three key components:

- An algorithm for the transmitted patient data to identify critical values or missing data, which allows for an immediate identification of the patients requiring immediate (medical) attention,
- Telecommunication software for a direct communication between TMC staff, patients, GPs, and local cardiologists, as well as
- Electronic health records for all relevant medical information (e.g. medication plan; reports about previous hospitalisation; laboratory data).

Patients are provided with a mobile phone (DORO Easy 510/Doro HandlePlus 334gsm, Doro AB) to call the TMC directly in case of emergency. In such situations, it is also possible to initiate a live ECG stream using the ECG device. The tablet uses the mobile network to transmit the patient data automatically in an encrypted manner (GSM-encryption via VPN-Tunnel) to a central server of the TMC in Berlin provided by project partner Deutsche Telekom AG. The combination of measurements and personal data

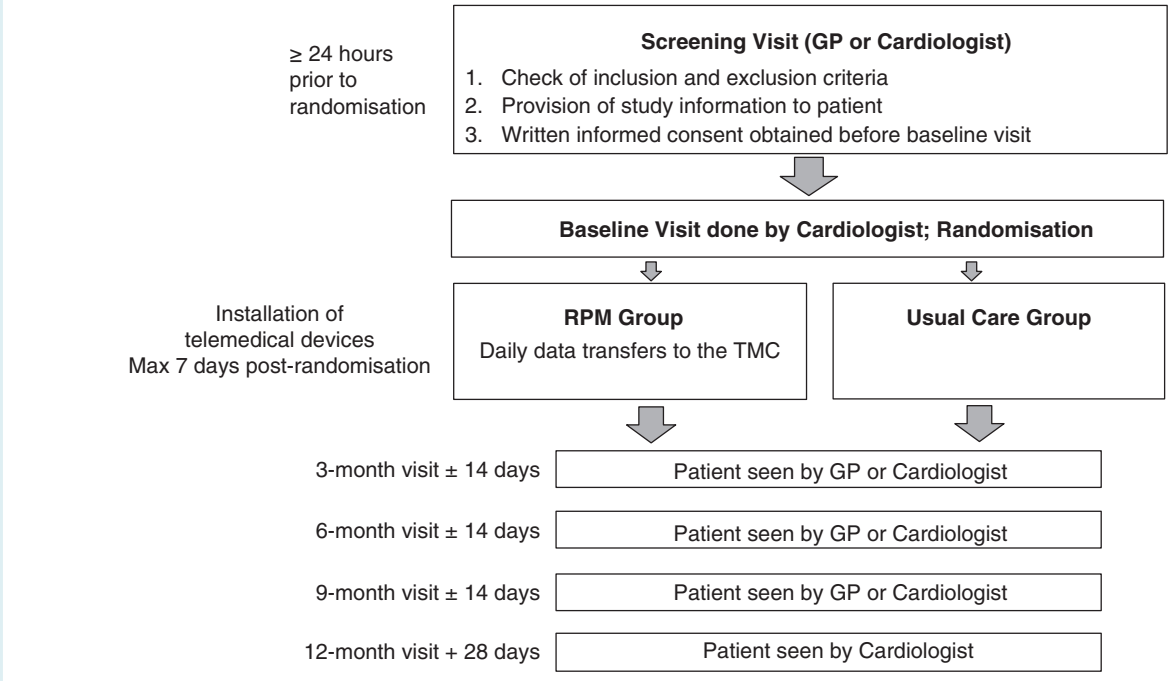

Figure 1 Trial flowchart. GP, general practitioner; RPM, remote patient management; TMC, telemedical centre.

with distinct information codes are only executed at a server at the Charité - Universitätsmedizin Berlin. To ensure patient safety, it is required a priori that the average transmission time to get the data to the TMC must be < 90 s. The availability of the mobile network connection is provided by the provider Deutsche Telekom AG. The complete data collection process, transmission and processing is done in strict compliance with state-of-the-art confidentiality and technical standards as agreed with and certified by the relevant data protection officer. For authentication of the individual measurements, all data transmissions incorporated unique device identification information. A service level agreement with the technical provider is concluded for first and second level support and corresponding service and escalation concepts.

In February 2013, the system was successfully tested in terms of safety, stability and performance during a pilot study done over 1 month in healthy volunteers at 50 different sites in rural (Brandenburg) and metropolitan areas (Berlin). The main outcome of the pilot study was a total system availability > 99%. The Fontane system obtained a European Conformity marking (CE) in 2013.

Registered nurses of the TMC install the telemonitoring equipment and train the patients and their families during home visits within 7 working days after randomisation. In addition, the nurses assess patients' self-care capabilities, give them information about their chronic disease (nursing assessment) and initiate a HF patient education programme, which is continued with monthly structured telephone interviews. According to the study protocol, the patients are instructed to measure daily, blood pressure, ECG tracing SpO_2, body weight and self-rated health status on a 5-point Likert scale using the tablet interface at defined time intervals.

All patients receive UC for the treatment and management of HF at the discretion of their treating physician.[13]

24/7 Telemedical support

The TMC provides physician-led medical support 24/7 for the entire study period according to standard operating procedures.

Within the Fontane system, algorithms are programmed and run on the transmitted data. The output is used by the TMC physicians and nurses to prioritise the workload and workflow so that patients presenting with any of the data cut-off limits as shown in *Table 3* are managed with priority.

Monthly, a structured telephone contact between the nurses and the patient is planned to discuss disease status, assess symptoms of depression or any other illness. In addition, the telemedical staff members initiate telephone contact when deemed appropriate — e.g. when there are changes in disease status, in case of technical problems, to verify vital sign measurements, to give advice, or to institute or change concomitant treatments.

Biomarker-guided approach

At the baseline visit and at each follow-up visit, biomarkers are taken and analysed by an independent laboratory. The results are sent to the CTC and the TMC. According to defined cut-off values for mid-regional pro-adrenomedullin (MR-proADM), patients are risk categorised as follows: low risk patients (MR-proADM ≤ 1.2 nmol/L) and high risk patients (MR-proADM > 1.2 nmol/L).

Table 2 Study flow

	Screening	Baseline	3-Month visit	6-Month visit	9-Month visit	Final visit (365 days or within + 28 days)
Informed consent and patient information	X	X				
Review inclusion/exclusion criteria	X	X				
Randomisation		X				
Physical examination		X				X
Registration medication		X				X
Echocardiography		X				
12-channel ECG		X				X
Laboratory tests: haemoglobin, haematocrit, leucocytes, thrombocytes, sodium, potassium, creatinine		X	X	X	X	X
Cardiac biomarkers: NT-proBNP, MR-proADM, MR-proANP, procalcitonin		X	X	X	X	X
Health questionnaires: MLHFQ, EQ-5D-3 L, PHQ-9D, G9-EHFScBS		X				X
Registration of events: hospitalisation, emergency, death			X	X	X	X

EQ-5D-3 L, EuroQol-5 Dimensions-3 Levels; G9-EHFScBS, German 9-Item European Heart Failure Self-care Behaviour Scale; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-A type natriuretic peptide; NT-proBNP, N-terminal pro-B type natriuretic peptide; PHQ-9D, Patient Health Questionnaire nine questions in German.

Table 3 Algorithm-guided prioritisation rules of the incoming vital parameters in the Fontane software

- Bradycardia, heart rate < 50 b.p.m.
- Tachycardia, heart rate > 100 b.p.m.
- Ventricular tachycardia
- New-onset atrial fibrillation
- PQ interval > 200 ms
- QRS duration ≥ 120 ms
- QTc interval > 460 ms
- SpO_2 < 94%
- Body weight (weight gain > 1 kg in 1 day, > 2 kg in 3 days; > 2.5 kg in 8 days)
- Blood pressure systolic: < 90 or > 140 mmHg; diastolic < 40 or > 90 mmHg
- Self-rated health status (grades from 1-very good to 5-very bad): deterioration of about 2 grades starting from 1, or grade 4 or 5)

SpO_2, peripheral capillary oxygen saturation.

High risk patients are primarily followed by TMC physicians ('doctors care'), and low risk patients by registered TMC nurses ('nurse care'). After each follow-up visit, patients are categorised in accordance with the new biomarker sample results.

Concomitant medication review

Patients allocated to the RPM group undergo a daily structured review of their concomitant medications based on the transmitted data. In consent with the study site physicians, the TMC physicians will optimise concomitant treatments as appropriate to achieve the following targets:

- Heart rate < 75 b.p.m. for patients in sinus rhythm.
- Blood pressure control: systolic < 140 mmHg and diastolic < 90 mmHg.
- Patients with new-onset atrial fibrillation: use of anticoagulant therapy as a long-term treatment and antiarrhythmic therapy.
- Patients in NYHA class II–IV: instigate the use of mineralocorticoid receptor antagonists where possible.

The aim is to ensure that patients are prescribed the maximally tolerated doses to achieve these targets and, in addition, diuretic doses are adapted in case of weight gain and worsening symptoms.

The telemedical team informs the patients' GP or caring physician by telephone, fax or email about any new events or important clinical findings from the monthly telephone contact, contacts with the emergency doctor, or any intervention made to the patients' therapy as a result of measured telemedical vital parameters. The TMC only advices the patient's primary physician — it is the latter who has the overall responsibility to instigate the medical management of the patients.

Other data collection processes

To avoid information collection bias, given the daily contact with patients in the RPM group, we have implemented a quality control process to ensure the accurate and complete reporting of hospitalisations in both the RPM and UC groups. Patients are asked to sign an informed consent including their permission for the TMC to contact their health insurance company to cross check the hospitalisations reported by the investigators with those on file in the health insurance records. This process was approved by the German Federal Social Insurance Office, Bonn.

Study outcomes

The primary outcome is the days lost (%) due to unplanned cardiovascular hospitalisations or all-cause death, comparing RPM with UC only during the individual follow-up time.

The main secondary outcomes include:

a. All-cause mortality during the individual follow-up time (+ 28 days from the final study visit to a maximum of 393 days).
b. Cardiovascular mortality during the individual follow-up time (+ 28 days from the final study visit to a maximum of 393 days).
c. Days (%) lost due to unplanned cardiovascular hospitalisations during the individual follow-up time.
d. Days (%) lost due to HF hospitalisations during the individual follow-up time.
e. Change in the Minnesota Living with Heart Failure Questionnaire (MLHFQ) Global score between baseline and 365 days.
f. Change in the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and of MR-proADM between baseline and 365 days.

The following recurrent event analyses will be performed:

a. Unplanned cardiovascular hospitalisations and cardiovascular mortality.
b. Unplanned cardiovascular hospitalisations and all-cause mortality.
c. Unplanned HF hospitalisations and cardiovascular mortality.
d. Unplanned HF hospitalisations and all-cause mortality.

Pre-specified subgroups

Subgroup analyses will be performed for the primary outcome to assess the consistency of intervention effects across the following subgroups:

- Metropolitan vs. rural area of medical care.
- Male vs. female.
- Above/below median age.
- LVEF $\leq$ 45% vs. LVEF > 45%.
- NYHA functional class I/II vs. III/IV.
- Cardiac resynchronisation therapy (CRT) at baseline yes/no.
- Implantable cardioverter defibrillator (ICD) at baseline yes/no.
- MR-proADM at baseline $\leq$ 1.2 nmol/L vs. > 1.2 nmol/L.
- Tertiles of NT-proBNP baseline levels.
- Estimated glomerular filtration rate groups < 30/30–60/ > 60 mL/min.

Statistical considerations

Sample size

The sample size calculation was based on a subgroup of 333 patients of the TIM-HF trial (NCT00543881) with Patient Health Questionnaire (PHQ-9D) score < 10 and a hospitalisation due to decompensated HF within 12 months before randomisation.[7] At month 6, this subgroup of patients showed a 55% difference in the endpoint days lost due to unplanned cardiovascular hospitalisations and death in favour of the telemedical patients while at the 12-month follow-up time point, this difference was 36%. Based on these results of TIM-HF, a sample size of 1500 patients is planned for TIM-HF2 with an equal group size of 750 patients in the RPM and UC groups to detect a reduction in the primary outcome of 38% with a two-sided alpha of 5% with a power of 80%.

Statistical analyses

All analyses will be performed using the Full Analysis Set (FAS) in accordance with the intention-to-treat principle. Patients who are randomised to the RPM group, but for whom the RPM intervention was not installed, will be replaced.

The per protocol population will be a subset of the FAS population and will only include those patients with no major protocol deviation.

Analysis methods

Due to the expected skewed distribution, the primary outcome will be tested using a permutation test with weighting for the amount of follow-up time. All-cause and cardiovascular mortality will be analysed by Kaplan–Meier curves and log-rank tests. Cardiovascular mortality will be analysed taking competing risks into account with cumulative incidence curves and cause-specific hazard ratios. Recurrent events will be analysed by negative binomial tests, with sensitivity analysis according to WLW method or joint frailty models. Quality of life and biomarkers will be analysed by analysis of covariance. Further details will be given in a separate statistical analysis plan.

Individual patient follow-up will be defined as the time between randomisation and the actual or planned final study visit, which should take place plus maximally 28 days after day 365, i.e. a maximum of 393 days after randomisation. For patients who die before day 365, their intended follow-up will be calculated up to day 365. For patients who withdraw from follow-up prematurely — i.e. withdraw consent for further participation — their intended follow-up will be calculated up to the day of withdrawal of informed consent.

For the mortality-related secondary outcomes, the expanded individual follow-up time is defined as the time as of randomisation to the final study visit date + 28 days to a maximum of 393 days.

Discussion

The TIM-HF2 trial can be categorised as an RPM trial using non-invasive multi-parameter telemonitoring technology. The home telemonitoring devices for vital parameter measurement we implement for this trial have already been used in the TIM-HF study.[6,7]

Remote patient management devices come in different ways. Some implantable devices (e.g. CRT/ICD devices) today have remote data transfer functionality and these data can be used for RPM. Several other systems exist that use body weight or blood pressure data for RPM purposes. The home monitoring devices we use in TIM-HF2 are commercially available, but the system of systematic data processing and the TMC infrastructure we use is innovative. To the best of our knowledge, the combination of a vital parameter transfer from the home of the patient to an analytical machine in a TMC is used for the very first time under the conditions of a RPM clinical trial. In this setting, the TMC staff collaborates with a multidisciplinary team of health care providers (including cardiologists, nurses, and GPs) as well as the patient. The identification of high and low risk patients is supported by the use of biomarker data. This holistic approach also aims to increase adherence to the pharmacologic HF treatment.[16]

Selection of the population to be included in the TIM-HF2 trial

Based on our experiences in the TIM-HF study,[6,7] we extensively evaluated the data to identify the most optimal HF subpopulation that could potentially best benefit from this type of health care management, and the best endpoint to study. In the TIM-HF trial, the patients that seemed to fair better were patients who had a recent hospitalisation for HF and who did not present with major depression as defined by the German Version of the PHQ-9 (PHQ-9D) score. The patient selection criteria in the TIM-HF2 trial reflect these findings.

Another important factor of consideration when determining the best treatment strategy for HF patients is their domicile — i.e. rural or urban. In contrast to metropolitan areas with relatively easy access to a high number of cardiologists, rural area HF care in Germany is dominated by GPs.[17] Stakeholders have the expectation that RPM will be able to provide the same level of care and access to specialised care as that easily accessible in a metropolitan setting. We took this factor into consideration when designing the TIM-HF2 trial, and hence we aim to have a proportion of more than 60% of sites located in rural areas.

Rationale for the selection of the primary outcome

We selected the primary outcome as days (%) lost due to unplanned cardiovascular hospitalisations and all-cause mortality for two reasons. It is an appropriate outcome in RPM trials in HF patients, which was first used as a primary endpoint in the Trans-European Network Home-Care Management System (TEN-HMS) study.[18] Moreover, the primary outcome of TIM-HF2 is a patient centric outcome by definition, reflecting the most key patient expectations for his/her HF care, i.e. to be alive and to remain outside the hospital.

If this primary endpoint is positive, the TIM-HF2 trial would demonstrate that RPM with integrated biomarker assessment is beneficial for a large subgroup of HF patients following recent hospitalisation and excluding those with evidence of major depression. Importantly, the study includes patients with reduced, mid-range and preserved LVEF.[19,20]

We believe that this real-time approach to the management of specific HF populations is the way forward to provide timely, personalised and quality care to this chronically ill patient population. Both the education and the involvement of patients in the HF management and treatment strategy may also help in preventing a 'full-blown' manifestation of a worsening HF episode as patients will be able to identify worsening signs and symptoms early. The results of our study are expected in 2018.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Study Committees.

Appendix S2. Clinical event classification criteria.

Appendix S3. List of primary site investigators, nurses and study management.

Table S1. Stratification factors for the minimisation process in randomisation as per Pocock's minimisation algorithm for TIM-HF2.

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References

1. Cowie MR, Anker SD, Cleland JG, Felker GM, Filippatos G, Jaarsma T, Jourdain P, Knight E, Massie B, Ponikowski P, López-Sendón J. Improving care for patients with acute heart failure: before, during and after hospitalization. *ESC Heart Fail* 2014;**1**:110–145.
2. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* 2016;**18**:242–252.
3. Anker S, Koehler F, Abraham W. Telemedicine and remote management of patients with heart failure. *Lancet* 2011;**378**:731–739.
4. Ong MK, Romano PS, Edgington S, Aronow HU, Auerbach AD, Black JT, De Marco T, Escarce JJ, Evangelista LS, Hanna B, Ganiats TG, Greenberg BH, Greenfield S, Kaplan SH, Kimchi A, Liu H, Lombardo D, Mangione CM, Sadeghi B, Sadeghi B, Sarrafzadeh M, Tong K, Fonarow GC; Better Effectiveness After Transition–Heart Failure (BEAT-HF) Research Group. Effectiveness of remote patient monitoring after discharge of hospitalised patients with heart failure: The Better Effectiveness After Transition–Heart Failure (BEAT-HF) randomized clinical trial. *JAMA Intern Med* 2016;**176**:310–318.
5. Hofmann R, Voeller H, Nagels K, Bindl D, Vettorazzi E, Dittmar R, Wohlgemuth W, Neumann T, Stork S, Bruder O, Wegscheider K, Nagel E, Fleck E. First outline and baseline data of a randomized, controlled multicenter trial to evaluate the health economic impact of home telemonitoring in chronic heart failure - CardioBBEAT. *Trials* 2015;**16**:343.
6. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Bohm M, Boll H, Baumann G, Honold M, Koehler K, Gelbrich G, Kirwan BA, Anker SD; Telemedical Interventional Monitoring in Heart Failure Investigators. Impact of remote telemedical management on mortality and hospitalisations in ambulatory patients with chronic heart failure: the Telemedical Interventional Monitoring in Heart Failure study. *Circulation* 2011;**123**:1873–1880.
7. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Bohm M, de Brouwer S, Perrin E, Baumann G, Gelbrich G, Boll H, Honold M, Koehler K, Kirwan BA, Anker SD. Telemedicine in heart failure: pre-specified and exploratory subgroup analyses from the TIM-HF trial. *Int J Cardiol* 2012;**161**:143–150.
8. Morgan JM, Kitt S, Gill J, McComb JM, Ng GA, Raftery J, Roderick P, Seed A, Williams SG, Witte KK, Wright DJ, Harris S, Cowie MR. Remote management of heart failure using implantable electronic devices. *Eur Heart J* 2017;**38**:2352–2360.
9. Böhm M, Drexler H, Oswald H, Rybak K, Bosch R, Butter C, Klein G, Gerritse B, Monteiro J, Israel C, Bimmel D, Käab S, Huegl B, Brachmann J; OptiLink HF Study Investigators. Fluid status telemedicine alerts for heart failure: a randomized controlled trial. *Eur Heart J* 2016;**37**:3154–3163.
10. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, Brachmann J, Lewalter T, Goette A, Block M, Kautzner J, Sack S, Husser D, Piorkowski C, Sogaard P; IN-TIME Study Group. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. *Lancet* 2014;**384**:583–590.
11. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS, CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011;**377**:658–666.
12. Van Spall HGC, Rahman T, Mytton O, Ramasundarahettige C, Ibrahim Q, Kabali C, Coppens M, Brian Haynes R, Connolly S. Comparative effectiveness of transitional care services in patients discharged from the hospital with heart failure: a systematic review and network meta-analysis. *Eur J Heart Fail* 2017;**19**:1427–1443.
13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
14. Adamson PB, Ginn G, Anker SD, Bourge RC, Abraham WT. Remote haemodynamic-guided care for patients with chronic heart failure: a meta-analysis of completed trials. *Eur J Heart Fail* 2017;**19**:426–443.
15. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975;**31**:103–115.
16. Komajda M, Cowie MR, Tavazzi L, Ponikowski P, Anker SD, Filippatos GS; QUALIFY Investigators. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail* 2017;**19**:1414–1423.
17. Meinertz T, Hamm C, Schlensak C, Fleck E, Cremer J, Stiller B, Schmalz AA, Wegscheider K, Friede T, Heinemann M, Kelm M, Welz A, Ertl G, Gummert J, Kuck KH, Markewitz A, Voller H, Weinbrenner S, Falk J, Stang A, Stang M, Ensminger S, Dewald O, Eschenhagen T. *Deutscher Herzbericht 2017. 29. Bericht/Sektorenübergreifende Versorgungsanalyse zur Kardiologie, Herzchirurgie und*

Kinderherzmedizin in Deutschland. Frankfurt am Main: Deutsche Herzstiftung; 2018.
18. Cleland JG, Louis AA, Rigby AS, Janssens U, Balk AH; TEN-HMS Investigators. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: the Trans-European Network-Home-Care Management System (TEN-HMS) study. *J Am Coll Cardiol* 2005;**45**: 1654–1664.
19. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1574–1585.
20. Delepaul B, Robin G, Delmas C, Moine T, Blanc A, Fournier P, Roger-Rolle A, Domain G, Delon C, Uzan C, Boudjellil R, Carrie D, Roncalli J, Galinier M, Lairez O. Who are patients classified within the new terminology of heart failure from the 2016 ESC guidelines? *ESC Heart Fail* 2017;**4**:99–104.